Synthesis and Structure of 5-Oxo-1-phenylpyrazoline-3- and 4-alkanoic Acids. Antiinflammatory Agents.

Franklin W. Short and Ernest J. Schoeb

Department of Chemistry, Division of Medical and Scientific Affairs, Parke, Davis and Company

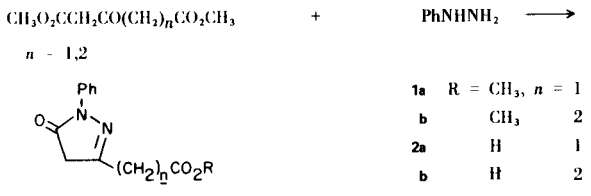
Condensation of appropriate β-keto esters with phenylhydrazine gave 5-oxo-1-phenyl-2-pyrazoline-3-and 4-alkanoic esters **1** and **3** which were saponified to the corresponding alkanoic acids **2** and **4**. Analogous condensation of the same β-keto esters with hydrazobenzene gave 5-oxo-1,2-diphenyl-3-pyrazoline-3-and 4-alkanoic esters **5** and **7** which were similarly converted to acids **6** and **8**. The structures of the oxopyrazolines as revealed by their infrared absorption are discussed, and results of their antiinflammatory screening are reported.

We have previously disclosed the synthesis of antiinflammatory 1,5-diarylpyrrole-2-propionic acids and reported in detail the preparation of some related 5-aryl-2-furan and oxazolepropionic acids (1). In this paper we describe the synthesis of some analogous 5-oxopyrazolines (**1-8**), discuss their structures as indicated by infrared absorption, and report the results of their evaluation as potential antiinflammatory agents.

Synthesis.

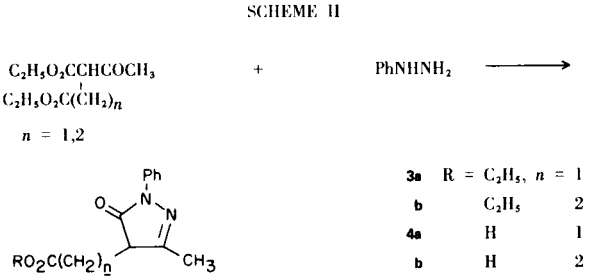
5-Oxo-1-phenyl-2-pyrazoline-3-acetic and propionic acids (**2**) were prepared as shown in Scheme I. Condensation of the appropriate β-keto esters with a molar equivalent of phenylhydrazine at 100° gave the oxopyrazoline methyl esters **1**, a procedure already reported for **1b** (2) and both analogous ethyl esters (3). Ester **1a** has been prepared previously by condensation of dimethyl pentadienedioate with phenylhydrazine (4). Saponification of the acidic oxopyrazoline esters **1** with excess base gave the carboxylic acids **2**, the propionic acid **2b** being isolated as the monohydrate. The acetic acid **2a** has been reported previously (3a,4).

SCHEME I



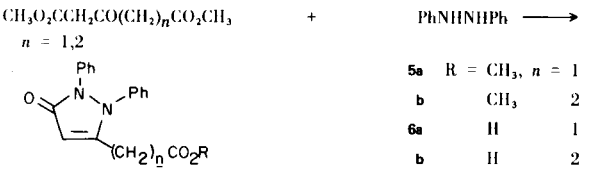
3-Methyl-5-oxo-1-phenyl-2-pyrazoline-4-acetic and propionic acids (**4**) were prepared similarly as shown in Scheme II. Condensation again of the appropriate β-keto ester with phenylhydrazine at 100° gave the oxopyrazoline ester **3a**, previously prepared by cyclization of the intermediate phenylhydrazone at 150° (5) and 170° (6). In the case of **3b**, 100° (for 2 hours) was insufficient to achieve cyclization to the oxopyrazoline but the product was obtained from reaction of the keto ester and phenylhydrazine in boiling glacial acetic acid. Ester **3b** has been prepared previously by distillation of the intermediate phenylhydrazone (7). Saponification of the crude esters **3** gave the carboxylic acids **4**, the propionic acid **4b** being characterized as the hemihydrochloride hemihydrate. The acetic acid **4a** has been reported previously as the anhydrous base (5) and as the monohydrate (6).

SCHEME II



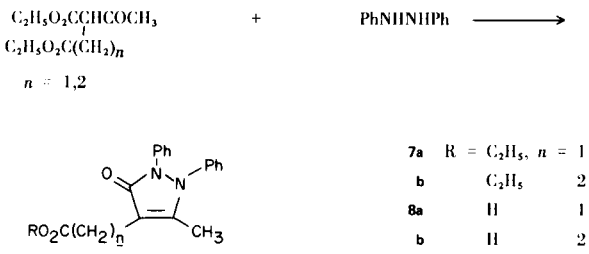
5-Oxo-1,2-diphenyl-3-pyrazoline-3-acetic and propionic acids (**6**) were prepared as shown in Scheme III. Condensation of the appropriate β-keto esters with a molar equivalent of hydrazobenzene at about 150° (8) or in boiling glacial acetic acid gave the oxopyrazoline esters **5**. von Perger (9) has reported the analogous condensation of diethyl 3-oxoglutarate (n = 1) with hydrazobenzene but assigned an incorrect structure to the product (10). Saponification of the crude esters **5** gave the carboxylic acids **6**; however, the β,γ-unsaturated acid **6a** decarboxylated readily during isolation and was not obtained pure. von Perger (9, *cf.* 10) has reported conversion of the ethyl ester analogous to **5a** to the corresponding 3-methylpyrazoline by decarboxylation of the intermediate acid **6a** but did not describe the acid.

SCHEME III



3-Methyl-5-oxo-1,2-diphenyl-3-pyrazoline-4-acetic and propionic acids (**8**) were prepared similarly as shown in Scheme IV. Condensation again of the appropriate β-keto esters with hydrazobenzene at about 150° gave the oxopyrazoline esters **7**, and saponification of the crude esters gave the carboxylic acids **8**. The acetic acid **8a** has been prepared previously from the corresponding 4-acetylpyrazoline by the Willgerodt-Kindler reaction (11).

SCHEME IV

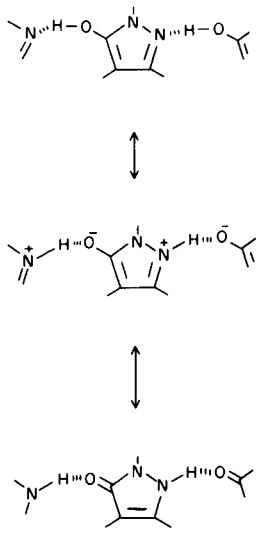


Structure.

The oxopyrazolines described (except **1a** and **7b**) were characterized by their infrared absorption, and our observations and interpretation are in general accord with previous discussions of similar compounds by Refn (12) and Katritzky and Maine (13).

That the tautomeric 5-oxo-1-phenyl-2-pyrazoline esters **1** and **3** in chloroform solution (acids **2** and **4** are insoluble) exist at least predominately in the 5-oxo-2-pyrazoline form is evidenced primarily by a strong ring carbonyl stretching vibration in the range 1711-1716 cm^{-1} (Table I). However, the 4-substituted pyrazolines **3** are not entirely in this form as indicated by weak, broad hydrogen-bonding absorption at 2500-3400 cm^{-1} (*cf.* 13). In potassium bromide, esters **1** and **3**, and acids **2** and **4**, lack the ring carbonyl band and show instead strong hydrogen-bonding vibrations in the 2400-2800 cm^{-1} region and different ring-stretching vibrations in the 1500-1650 cm^{-1} region (Table I). Within the limitations of conventional symbolism, the predominant tautomeric form in the solid state is probably best represented as the polymeric hydrogen-bonded structure shown in Table I, a composite (14) of the resonance structures (12,13) shown in Scheme V in which the 5-oxo-3-pyrazoline form is least, if at all, important.

SCHEME V



The 5-oxo-1,2-diphenyl-3-pyrazolines **5-8** are not tautomerically ambiguous. Their spectra are characterized by a conjugated ring carbonyl vibration band in the 1660 cm^{-1} region, and are similar whether the sample is a liquid film, potassium bromide disk, or chloroform solution (Table II). The two broad bands observed for **6** in the acid dimer region are similar to those seen in the benzoic acid-pyridine system (*cf.* 12), and suggest interaction between the carboxyl group and the basic ring nitrogen atom.

Antiinflammatory Screening.

The oxophenylpyrazolinealkanoic acids (except **6a**) were screened as potential antiinflammatory agents by assessing their ability to delay the appearance of ultraviolet light-induced erythema on the skin of depilated albino guinea pigs (15). All were inactive at 200 mg./kg. when administered by gavage dissolved in aqueous hydrochloric acid (**2a**) or sodium hydroxide (all others).

EXPERIMENTAL

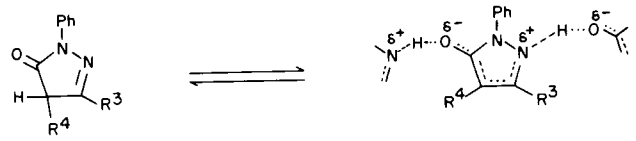
The ethanol used was 3A denatured, the petroleum ether was low boiling (distillation range about 30-60°). Melting points were observed in open capillary tubes in a calibrated Thomas-Hoover apparatus and the values were recorded without correction. Infrared absorption spectra were recorded on a Beckman IR7 or 9 spectrophotometer and data are given in the Tables.

5-Oxo-1-phenyl-2-pyrazoline-3-acetic Acid (**2a**) and Methyl Ester (**1a**).

Phenylhydrazine (9.9 ml., 0.100 mole) was added at a rapid dropwise rate to 17.4 g. (0.100 mole) of dimethyl 3-oxoglutarate with swirling during which the temperature rose to about 70°, and the resulting mixture was heated on a steam bath (open flask) for 1.5 hours. The glassy product obtained on cooling was crystallized from 100 ml. of methanol-100 ml. of water (additional

TABLE I

Infrared Absorption Bands in the Bond Stretching Region Above 1500 Cm^{-1} and Structural Assignments for 5-Oxo-1-phenyl-2-pyrazolines **1-4** (a).

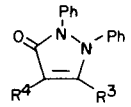


Compound	Substituents R^3	Substituents R^4	Medium	N-H-O bonding and CO_2H dimer	Carbonyl CO_2R	Carbonyl Ring	Pyrazole (-ine) and Ph ring multiple bonds
1b	$(CH_2)_2CO_2CH_3$	H	$CHCl_3$	-	1738s	1716s	1615b; 1599
			KBr	2400-2800	1736s	-	1618s; 1595s; 1565s
2a	CH_2CO_2H	H	KBr	2200-3200	1713s	-	1594s; 1558s; 1526s
2b	$(CH_2)_2CO_2H$	H	KBr	2200-3200	1721s	-	1603s,b; 1594s; 1570s,b
3a	CH_3	$CH_2CO_2C_2H_5$	$CHCl_3$	2500-3400	1734s	1711s	1645b; 1599s; 1537
			KBr	2400-2800	1730s	-	1630s; 1606s; 1592s; 1585s; 1520
3b	CH_3	$(CH_2)_2CO_2C_2H_5$	$CHCl_3$	2500-3400	1725s,sh	1714s	1645b; 1600; 1535
4a	CH_3	CH_2CO_2H	KBr	2200-3200; 1850-2100	1720s	-	1605s; 1568s
4b	CH_3	$(CH_2)_2CO_2H$	KBr	2200-3200	1741s; 1707s	-	1598s; 1563

(a) Frequencies in cm^{-1}. Band characteristics: s, strong; b, broad; sh, shoulder. Compound **3b** is unpurified material; **4b** is the hemihydrochloride.

TABLE II

Infrared Absorption Bands in the Bond Stretching Region Above 1500 Cm^{-1} and Structural Assignments for 5-Oxo-1,2-diphenyl-3-pyrazolines **5-8** (a).



Compound	Substituents		Medium	CO_2H dimer	Carbonyl		Pyrazoline and Ph ring multiple bonds
	R^3	R^4			CO_2R	Ring	
5a	$CH_2CO_2CH_3$	H	$CHCl_3$	-	1744s	1663s	1620s; 1597s; 1520sh
5b	$(CH_2)_2CO_2CH_3$	H	liq. film	-	1738s	1663s,b	1602s; 1525b
6a	CH_2CO_2H	H	$CHCl_3$	2400-3500; 1850-2000	1722	1666s	1625b; 1596s
			KBr		1720	1640s,b	1596s; 1543b
6b	$(CH_2)_2CO_2H$	H	$CHCl_3$	2400-3300; 1850-2200	1722	1665	1624s; 1588s
			KBr		1735s	1670sh	1620s; 1591s; 1583s
7a	CH_3	$CH_2CO_2C_2H_5$	liq. film	-	1737s	1681	1655b; 1598; 1551
8a	CH_3	CH_2CO_2H	$CHCl_3$	2200-3300	1739s	1660	1612; 1581s
			KBr		1710s	1671	1624; 1607s; 1578s
8b	CH_3	$(CH_2)_2CO_2H$	$CHCl_3$	2400-3300	1733sh; 1715	1656s	1620; 1596s; 1588s,sh
			KBr		1717s	1660sh	1625s; 1620s; 1589s; 1583s

(a) Frequencies in cm^{-1}. Band characteristics: s, strong; b, broad; sh, shoulder. Compounds **5**, **6a**, and **7a** are unpurified materials; **6a** is partially decarboxylated.

methanol was added as needed to reverse clouding) to give 14.4 g. (62%) of **1a**, m.p. 86.5-89° [lit. (4) m.p. 92-93°].

A solution of 14.3 g. (0.062 mole) of ester **1a** (m.p. 86.5-89°) in 150 ml. (0.150 mole) of 1*N* sodium hydroxide was heated on a steam bath for 1 hour, chilled, and acidified by dropwise addition of a solution of 12.4 ml. (0.15 mole) of concentrated hydrochloric acid in 15 ml. of water until separation of the gummy product was complete (final pH about 3). The mixture was kept overnight at room temperature, the solidified precipitate was ground, collected, washed with cold water and dried to give 10.6 g. (79%) of product, m.p. 129-132° (effervescence). Crystallization from 350 ml. of water (charcoal) gave 5.8 g. of **2a**, m.p. 131-132° (effervescence) [lit. (3a,4) m.p. 134°, 130-132°].

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.6; H, 4.6; N, 12.8. Found: C, 60.9; H, 4.5; N, 13.1.

5-Oxo-1-phenyl-2-pyrazoline-3-propionic Acid (**2b**) Monohydrate and Methyl Ester (**1b**).

Using essentially the same procedure described above for the preparation of **1a**, a mixture of 9.9 ml. (0.100 mole) of phenylhydrazine and 18.8 g. (0.100 mole) of dimethyl 3-oxohexanedioate was heated for 2.25 hours, the last 0.25 hour under reduced pressure. A solution of the crude material in 75 ml. of hot ethyl acetate (charcoal) was diluted with petroleum ether to give 12.3 g. (50%) of product, m.p. 78-80°. Recrystallization of 9.7 g. of product from 50 ml. of methanol-100 ml. of water (additional methanol was added as needed to reverse clouding) gave 8.0 g. of **1b**, m.p. 79-80.5° [lit. (2) m.p. 79-80°, 79.5°].

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7; N, 11.4. Found: C, 63.6; H, 5.6; N, 11.5.

A solution of 17.8 g. (0.072 mole) of ester **1b** (m.p. 75-79°) and 14.3 g. (0.22 mole) of U.S.P. potassium hydroxide in 140 ml. of methanol was kept at room temperature for 20.5 hours and concentrated. A stirred solution of the residue in 100 ml. of water was chilled and the product was precipitated by rapid dropwise addition of 170 ml. (0.170 mole) of 1*N* hydrochloric acid followed by 5 ml. (0.09 mole) of glacial acetic acid. The solid was collected, washed with cold water and dried at 45-60° under reduced pressure to give 16.5 g. (91%) of product (monohydrate) melting over a wide range to about 150°. Crystallization of this material, combined with 2.0 g. from a previous run, from 50 ml. of ethanol-300 ml. of water and drying at 70° under reduced pressure gave 16.5 g. of **2b** monohydrate, m.p. 151-153° after transitory softening at about 115°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3 \cdot H_2O$: C, 57.6; H, 5.6; N, 11.2; H_2O, 7.2. Found: C, 57.9; H, 5.7; N, 11.3; H_2O, 6.6, 7.0.

3-Methyl-5-oxo-1-phenyl-2-pyrazoline-4-acetic Acid (**4a**) and Ethyl Ester (**3a**).

Using essentially the same procedure described above for the preparation of **1a**, a mixture of 9.9 ml. (0.100 mole) of phenylhydrazine and 21.6 g. (0.100 mole) of diethyl acetylsuccinate was heated for 2 hours. Crystallization of the resulting oil from 50 ml. of ethyl acetate gave 15.9 g. (61%) of **3a**, m.p. 136.5-137.5° [lit. (5.6) m.p. 138°, 139-140°].

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.2; N, 10.8. Found: C, 64.8; H, 6.1; N, 10.9.

A solution of ester **3a** (0.1 mole of crude oil prepared as above) and 10.5 ml. (0.20 mole) of 50% sodium hydroxide in 100 ml. of water was heated on a steam bath for 1 hour, chilled and washed with ether (two 50-ml. portions). After heating and filtering, the chilled and stirred solution was neutralized by dropwise addition of a solution of 16.7 ml. (0.20 mole) of concentrated hydrochloric acid in 100 ml. of water. The solid was collected, washed with cold water and dried at 70° under reduced pressure to give 16.9 g. (73%) of product, m.p. 174-177° (effervescence). Crystallization from 700 ml. of water and drying as before gave 14.9 g. of **4a**, m.p. 177-178.5° [lit. (5a,6) m.p. 178°, monohydrate m.p. 180° (effervescence) after losing water at 100°].

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.1; H, 5.2; N, 12.1. Found: C, 62.1; H, 5.2; N, 11.9.

3-Methyl-5-oxo-1-phenyl-2-pyrazoline-4-propionic Acid (**4b**) Hemihydrochloride Hemihydrate and Ethyl Ester (**3b**).

A solution of 9.9 ml. (0.100 mole) of phenylhydrazine and 23.0 g. (0.100 mole) of diethyl 2-acetylglutarate in 50 ml. of glacial acetic acid was refluxed for 7 hours and concentrated at 70° under reduced pressure to give **3b** as an oil [lit. (7) b.p. 215° (3 mm.)]. When the reactants were merely heated together as was done in the preparation of **1a** and **-b** and **3a**, cyclization appeared not to have occurred as indicated by absence of absorption at 1714 cm^{-1} (ring C=O) in the ir spectrum of the crude product.

Using essentially the same procedure described above for the preparation of **4a**, ester **3b** (0.1 mole of crude oil) was saponified and the product was precipitated to give a taffy-like material which resisted attempts at crystallization or solid salt formation with amines and organic acids. A hot, filtered solution of the crude product in 100 ml. (0.100 mole) of 1*N* hydrochloric acid was kept overnight at room temperature. The precipitated solid was collected, washed with 1*N* hydrochloric acid and dried at room temperature under reduced pressure over calcium chloride to give 20.1 g. (74%) of product (hemihydrochloride hemihydrate) of indefinite m.p. Recrystallization from 70 ml. of 1*N* hydrochloric acid and drying as before gave 14.8 g. of **4b** hemihydrochloride hemihydrate, m.p. 80-82°, effervesces 140°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3 \cdot \frac{1}{2}HCl \cdot \frac{1}{2}H_2O$: C, 57.1; H, 5.7; Cl, 6.5; N, 10.2; H_2O, 3.3. Found: C, 57.1, 57.2; H, 5.8, 5.8; Cl, 6.9, 7.1; N, 10.2, 10.3; H_2O, 3.2, 2.9.

5-Oxo-1,2-diphenyl-3-pyrazoline-3-acetic Acid (**6a**) and Methyl Ester (**5a**).

Using essentially the same procedures described below for the preparation of **5-** and **6b**, a mixture of 18.4 g. (0.100 mole) of hydrazobenzene and 17.4 g. (0.100 mole) of dimethyl 3-oxoglutarate was heated at 130-155° for 2 hours to give **5a** as an oil. Saponification of the crude ester **5a** and concentration of the chloroform extract gave 15.7 g. of **6a** as a foamy residue which effervesced on heating. Extensive decarboxylation was confirmed by incomplete solution of the material in hot 1*N* sodium hydroxide and relatively weak carboxyl carbonyl absorption at 1722 cm^{-1}.

The initial condensation was repeated by refluxing a solution of 0.01 mole of both reactants in 5 ml. of glacial acetic acid for 0.5 hour. After 24 hours a mixture of this solution, 5 ml. of 50% sodium hydroxide and 50 ml. of water was extracted with benzene, and the washed and dried extract was concentrated to give 2.1 g. (68%) of **5a** as an oil. Saponification of the crude ester **5a** as before and careful acidification with 1*N* hydrochloric acid gave a fine precipitate which was collected (filtration was very slow and gas evolution was evident), washed with water and dried on the funnel to give 0.2 g. of **6a** melting about 130° (effervescence). Extensive decarboxylation was again confirmed by a relatively weak ir carboxyl carbonyl band.

5-Oxo-1,2-diphenyl-3-pyrazoline-3-propionic Acid (**6b**) and Methyl Ester (**5b**).

A mixture of 18.4 g. (0.100 mole) of hydrazobenzene and 18.8 g. (0.100 mole) of dimethyl 3-oxohexanedioate was stirred

and heated in an open flask to 130° over 25 minutes, then at 130-160° for 2 hours to give **5b** as an oil.

A solution of ester **5b** (0.1 mole of crude oil), 10.5 ml. (0.20 mole) of 50% sodium hydroxide and 20 ml. of water in 100 ml. of 95% ethanol was refluxed for 1 hour and concentrated. The residual slurry was diluted to about 125 ml. with water and filtered to give 8.6 g. (47% recovery) of hydrazobenzene. The aqueous alkaline filtrate was washed with ether and acidified with 20 ml. (0.24 mole) of concentrated hydrochloric acid. The resulting mixture was extracted with chloroform (100 and 30 ml.), and the extract was washed with water (two 50-ml. portions), dried over sodium sulfate and concentrated to give 15.8 g. of gummy product. Digestion of the crude product in 100 ml. of boiling ethyl acetate and filtration gave 3.8 g. of solid product, m.p. 179-182°; an additional 1.6 g., m.p. 181-184°, separated from the filtrate (total 5.4 g., 18%). Two crystallizations from methanol-water (12-18 and 20-30 ml.) gave 3.1 g. of **6b**, m.p. 184-186°.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2; N, 9.1. Found: C, 70.1; H, 5.3; N, 9.3.

3-Methyl-5-oxo-1,2-diphenyl-3-pyrazoline-4-acetic Acid (**8a**) and Ethyl Ester (**7a**).

A mixture of 18.4 g. (0.100 mole) of hydrazobenzene and 21.6 g. (0.100 mole) of diethyl acetylsuccinate was stirred and heated in an open flask at 150° for 7 hours to give **7a** as an oil.

Using essentially the same procedure described above for the preparation of **6b**, ester **7a** (0.1 mole of crude oil) was saponified to give 11.4 g. (37%) of solid product, m.p. 175-185°. Crystallization from 75 ml. of ethanol (charcoal) gave 4.6 g. of **8a**, m.p. 188-190.5° [lit. (11) m.p. 192°].

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2; N, 9.1. Found: C, 70.1; H, 5.2; N, 9.3, 9.2.

3-Methyl-5-oxo-1,2-diphenyl-3-pyrazoline-4-propionic Acid (**8b**) and Ethyl Ester (**7b**).

A mixture of 18.4 g. (0.100 mole) of hydrazobenzene and 23.0 g. (0.100 mole) of diethyl 2-acetylglutarate under nitrogen was stirred and heated to 150° over 1 hour and then at 140-155° for 6 hours to give **7b** as an oil.

Using essentially the same procedure described above for the preparation of **6b**, ester **7b** (0.1 mole of crude oil) was saponified and the aqueous alkaline solution obtained was added dropwise with stirring to a chilled solution of 25 ml. (0.30 mole) of concentrated hydrochloric acid in 100 ml. of water. The initially gummy precipitate gradually solidified and was collected, washed with water and dried to give 6.6 g. (21%) of product, m.p. 200-215°. Crystallization from 100 ml. of ethanol gave 4.8 g. of **8b**, m.p. 218-222°.

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.8; H, 5.6; N, 8.7. Found: C, 71.0; H, 5.4; N, 8.6.

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